REMARKS

A declaration (the "Brenan Declaration") of Dr. Colin Brenan, CEO of BioTrove, Inc., licensee of the present invention, accompanies this Response and is incorporated herein by reference.

Claims 1, 3-17, 41, and 44 are pending in the application, of which claims 1, 14, 16 and 41 are independent claims, while claims 3-13 depend directly or indirectly from claim 1, claim 15 depends from claim 14, claim 17 depends from claim 16, and claim 44 is multiply dependent upon claims 14, 16, and 41.

Claims 1, 3-15, 41 and 44 stand rejected under 35 U.S.C. 103(a) as unpatentable over de Macario (US Patent 4,682,890, hereinafter "de Macario") in view of Davis. Claims 16-17 (the other two pending claims), and also claim 44, stand rejected as unpatentable over de Macario in view of Davis and further in view of Böcker.

Claim 16 is amended to correct the reference to 'system' to properly reflect a 'method.' A typographical omission of the word 'to' is corrected in claim 44.

Rejections over Prior Art- De Macario ('890) in view of Davis and Böcker

Each of the independent claims (1, 14, 16, and 41) stands rejected over the combination of de Macario and Davis (with Böcker further applied against claim 16).

De Macario's device cannot accommodate resolution of holes on the scale required in claims 1, 14, 16, and 41. This proposition has been discussed in detail in Applicant's Response B of November 6, 2002 and is not contraverted. The present response is directed toward the combination of de Macario with other references upon which the Examiner bases all pending rejections.

It is Applicant's position that Davis may not be invoked to provide the hole density lacking in de Macario because Davis not only fails to address even the notion of a density of *samples* (how close one sample may be to one or more distinct samples), but also teaches a technology to which density of distinct samples is not even germane, and thus there can be no suggestion to combine the teachings of de Macario and Davis. This is discussed at greater length below.

De Macario teaches a plate for supporting fluid samples in a standard transmission spectrometer to replace conventional sample cuvettes. A device serving de

Macario's purpose is inherently incompatible with the teachings (and with the claims) of the present invention, and, more particularly, with a claimed density so high that it is impossible, using any method suggest by de Macario, to spatially resolve the contents of each through-hole in a standard spectrometer[1], and, therefore, de Macario *teaches away* from implementation of a density of through-holes such as taught by the present inventor.

Preliminary Clarification

Applicant wishes to clarify that the distinction of the present claims with respect to de Macario (alone or in combination with either of the other cited references) is *not* one of hole size, optimum value, or duplication of parts.

The claimed patentability of the present claims does not rest on considerations of through-hole size. A spectrometer may well detect and analyze light transmitted through a hole in an otherwise opaque surround, in a manner independent of the size of the hole, so long as contamination of the signal by an adjacent sample (i.e., cross-talk) is not a problem. Therefore, *In re Rose*, cited for the proposition that the size of an article is not a matter of invention is inapposite to the distinctions being raised in this case.

Moreover, the claimed novelty is not an optimum value among values otherwise recognized to be within the realm of possible practice for the application to which a cited reference is directed. The density claimed in the present claims, because of the diffraction spread of light transmitted through one of the holes, is far outside the range of any spatial resolution of a horizontal (or vertical) beam spectrophotometer, for reasons laid out in Applicant's Response B of November 6, 2002.

Thus, de Macario *cannot* be taken to suggest sample densities anywhere near those required by the methods claimed in the present invention, because de Macario uses conventional spectrometer optics suited to measurements based on standard cuvettes. Consequently, *In re Boesch*, cited for the proposition that discovery of the optimum value of a known result is not a matter of invention, is inapposite to the distinctions being raised in this case.

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[1] This applies no matter how the holes are indexed or advanced. Examiner's point with regard to alternate indexing mechanisms is well-taken but does not establish that any greater spatial resolution is suggested in any way by de Macario.

Finally, the distinction of the present claims over de Macario is not one of mere duplication of parts since it is not the *number* of holes alone that distinguishes the present invention over de Macario. Therefore, *In re Harza*, cited for the proposition that duplication of parts is within the skill of the "routineer" in the art, is also inapposite to the distinctions being raised in this case.

For convenience of discussion, salient and pertinent features of the primary and secondary cited references are laid out in the following table:

Summary of Teachings of Primary and Secondary References

De Macario	Davis and Böcker
Multiple through-holes	Mesh (or Net)
Hydrophobic surface treatment	Fill by dipping for homogenous specimen across all holes
Distinct samples	No cross-talk, dilution, or mixing jeopardy (because no distinct samples)
Spectrophotometer Sample Holder	No teaching of how or even whether individual holes might be filled with distinct samples
No teaching of sample density considerations	

Neither Davis nor Böcker can be applied, in combination with de Macario, to stand for density of samples absent in de Macario because neither Davis nor Böcker contemplates or suggests distinct liquid samples. Furthermore, no such a suggestion can be imputed as 'obvious' to a person of ordinary skill in the art.

One stated object of the present invention is that of handling vast numbers of compounds and reactions in parallel. (*See* Application, Background of the Invention.)

Faced with that object, together with the teachings of Davis, the task would be to increase the sample density from a *single homogenous film* to a high *density of distinct samples*. There is no hint in Davis that any such application is even conceivable, let alone 'suggested'.

Davis is directed toward support of a single film; all language in the application makes that abundantly clear. While Fig. 2 shows portions of the film spanning the holes, thereby governing the thickness, locally, of the film, there is no teaching that the solid

structure[2] **4** that bridges the mesh holes is dry, which is what would be required in order for the contents of adjacent holes to constitute distinct drops so that distinct samples could be accommodated.

It would be necessary to assume that the solid frame **4** of Davis is (or could be) 'dry' in order to invoke a combination of Davis with de Macario to stand for density of distinct samples. Yet, the Davis reference says otherwise. The 'support' that is the solid structure bridging the mesh holes, "is formed of a material which will not be attacked by either water or acidic components" by virtue of which "aqueous or acidic liquid specimens can be directly analyzed without the need of extracting in a solvent solution as used in the past." (Davis, col. 3, lines 39-43) I.e., the bridging structure is *wet*, which doesn't matter in the Davis application, because there is only a *single* sample (*one* per unit area) that is being analyzed.

Moreover, there can be no 'contamination' of one sample by a neighboring sample, because there is only a single sample. Similarly, there can be no cross-talk in the signals between samples, because, again, there is only a single sample.

For all these reasons, any suggestion, with hindsight of the invention of the present application, to the effect that "Davis is clearly capable of having individual samples placed in each through-hole" is traversed.

The Examiner is invited to consider whether it is obvious how to fill two adjacent pores of an ordinary window screen with two distinct liquid samples. Whether that is physically possible *at all* depends on the viscosity of the liquid, the size of the holes, and the thickness of the screen material, where the dependence on each of these characteristic quantities might be calculable (although that hasn't been shown) but cannot be said to be obvious. It is not clear that a droplet can be deposited in such a manner as to be suspended in a single screen pore without touching, and mixing (if the samples are miscible) with the contents of a neighboring pore.

Davis is silent as to the thickness of the mesh material (because Davis is not concerned with liquid communication between through-holes, as Davis contemplates a single film covering the entire mesh), so that considerations of whether multiple distinct samples might be supported in a window screen apply equally to the Davis device. They

[2] "Specimen support," in the parlance of the Davis patent.

also apply to the Böcker teaching which also, very explicitly (see Fig. 2) is based upon the analysis of a *single* sample.

The present application, on the other hand, describes, in detail, the aspect ratio of the through-holes, with typical representative proportions (2 mm depth; 200 μm diameter) called out in Fig. 5, for example. The present application further discusses (and claims) the surface treatment provided to prevent interdiffusion of the samples. These are neither matters of 'mere' design choice, nor can they be imputed to a person of ordinary skill at the time the present invention was made. Only *after* the teachings of the present invention could one contemplate a combination of the areal hole density of Davis with the distinct samples of de Macario. Nor is Böcker (albeit not cited for that purpose) of any avail to provide the density of distinct samples that is absent in de Macario.[3]

And, indeed, it has long been known that it would be 'desirable' to increase the throughput of assay processes. Brenan Declaration, ¶10.

A long-felt need that has gone unmet by extant technology prior to the present invention, is one 'secondary consideration' that must be considered in deciding whether or not a claimed invention is obvious. *See, In re* Huang, 40 USPQ2d 1685 (Fed. Cir. 1996) (PTO must consider objective evidence of nonobviousness). Indeed, objective considerations such as failure by others to solve the problem may often be the most probative and cogent evidence of nonobviousness. *Advanced Display Systems, Inc. v. Kent State University*, 54 USPQ2d 1673 (Fed. Cir. 2000).

Furthermore, the invention by the present inventor of a method whereby distinct samples may be captured and assayed in dense proximity, thereby enabling heightened throughput, has resulted in the licensing of the present invention (Brenan Declaration, ¶ 6) and, further, in the development and commercial success of a process based thereon

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[3] Böcker teaches a net for spreading out a single liquid sample over a defined area so that optical transmission through the net can be used to infer the amount of liquid located in a mesh and thus, by inference, the concentration of analytes in the single sample.

As with filling a window screen with distinct liquids in adjacent pores, there is no way to determine whether adjacent pores of the Böcker net could be filled with distinct samples, nor is there any suggestion to do so.

Thus Böcker is not "a method for analyzing a plurality of samples" nor can Böcker reasonably be suggested to be combined with a method for analyzing a plurality of samples (such as de Macario) to stand for separate analysis of optical radiation emanating from each through-hole, since all that is suggested by Böcker is counting (or, more correctly, inferring using pattern-recognition algorithms) whether a cell is full or empty in order to determine that aggregate quantity of a single liquid sample present in the film.

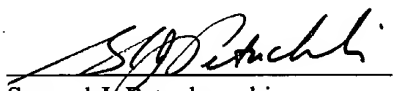
(Declaration, ¶¶ 6, 7, 15). The adoption of this technology, for the very reason that distinct samples may be collocated and analyzed at high spatial density, and the licensing of the present invention are described in the Brenan Declaration, ¶ 6.

It is the Examiner's position, as understood, that, by the time of the Davis reference, it had become possible to conduct a spectroscopic analysis on *a sample* as small as the contents of a single cell of the Davis mesh. However, there is no teaching that it had become possible to conduct spectroscopic analysis on a *density of samples* required in the present case, nor does either Davis or Böcker suggest that it might. And, indeed, as has been discussed, the known advantages of such a technology, were it to have been invented prior to the present invention, were well known.

Therefore, for these reasons, claim 1 (and dependent claims 3-13), claim 14 (and dependent claim 15), claim 16 and dependent claim 17, and claims 41 and 44 are all patentable over the references of record, separately or in combination.

Examination and allowance of the claims as amended is requested.

Respectfully submitted,



Samuel J. Petuchowski
Registration No. 31,970
Attorney for Applicant

Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110-1618
(617) 443-9292

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For: METHOD FOR PERFORMING MICROASSAYS

CLAIMS AS CURRENTLY PENDING

1. (Previously amended three times) A method for analyzing specified properties of a set of samples, the method comprising:

a. providing a platen having two substantially parallel planar surfaces, an inner layer of hydrophilic material, two outer layers of hydrophobic material coupled to opposite sides of the inner layer, and a two-dimensional array of a plurality of addressable through-holes, the through-holes being disposed substantially perpendicularly to the planar surfaces and the array characterized by an areal density of at least 1.6 through-holes per square millimeter;

b. loading a first sample into a first set of through-holes of the two-dimensional array, the first sample being a liquid;

c. retaining the first sample in the first set of through-holes by surface tension;

d. adding a second sample into a specified through-hole, the specified through-hole having at least one adjacent through-hole containing a sample other than the second sample, the specified through-hole further coinciding with one of the first set of at least one of the though-holes thereby permitting a reaction between the first sample and the second sample; and

e. characterizing the reaction in the through-hole in terms of the specified properties.

2. (Cancelled)

3. A method according to claim 1, wherein each through-hole is dimensioned so as to maintain a liquid sample therein by means of surface tension.

4. A method according to claim 1, wherein each through-hole has a volume less than 100 nanoliters.

5. (Previously twice amended) A method according to claim 1, wherein the first sample in liquid form includes at least one of a target in solution and a target in suspension.

6. (Previously twice amended) A method according to claim 1, wherein at least one of a target in solution and a target in suspension includes a biological material.

7. (Previously twice amended) A method according to claim 1, wherein the step of loading a first sample includes drawing the sample from a planar surface by capillary action.

8. A method according to claim 1, wherein the step of loading a first sample includes drawing the sample from a planar surface by capillary action.

9. A method according to claim 1, wherein the step of loading a first sample includes bringing the platen into contact with a reservoir of liquid and rotating the platen about an axis perpendicular to the surface of the reservoir.

10. A method according to claim 1, wherein the step of loading a first sample includes bringing the platen into contact with a reservoir of liquid and rotating the platen about at least one of an axis perpendicular to the surface of the reservoir and an axis parallel to the surface of the reservoir.

11. (Previously twice amended) A method according to claim 1, further including maintaining a humid atmosphere for preventing evaporation of the first sample.

12. (Previously twice amended) A method according to claim 1, further including coating the liquid sample with a monolayer for preventing evaporation of the first sample.

13. A method according to claim 1, further including coating the liquid sample with a monolayer for preventing evaporation of the first sample.

14. (Previously amended three times) A method for characterizing a plurality of samples of distinct composition, the method comprising:

a. providing a platen having a set of through-holes comprising a two-dimensional array with a density of at least 1.6 through-holes per square millimeter;

b. loading a specified sample into each through-hole of a first subset of the set of through-holes;

c. loading a second sample into at least one through-hole adjacent to a hole of the first subset of through-holes in such a manner as to substantially prevent capillary outmigration of the second sample; and

d. characterizing a property of the specified sample.

15. A method according to claim 14, the step of characterizing a property of the specified liquid sample comprising:

a. illuminating at least one through-hole of the subset of the set of through-holes with optical radiation; and

b. analyzing the optical radiation emanating from the at least one through-hole.

16. (Amended four times) A method for analyzing a plurality of samples, the [system] <u>method</u> comprising:

d. loading the samples into a plurality of through-holes disposed in a platen in a two-dimensional array characterized by an areal density of at least 1.6 through-holes per square millimeter;

e. illuminating a set of more than one of the plurality of through-holes with optical radiation; and

f. separately analyzing the optical radiation emanating from each through-hole of the set of more through-holes than one using an optical arrangement including a detector array.

17. (Previously amended) A method in accordance with claim 16, wherein the step of analyzing includes spectrally characterizing the optical radiation emanating from the plurality of through-holes.

41. (Previously amended) A method for characterizing a plurality of samples, the method comprising:

a. providing a platen having a two-dimensional array of through-holes;

a. loading a specified sample into each through-hole of a subset of the set of through-holes with a density of at least 1.6 through-holes per square millimeter; and

b. characterizing a property of the specified sample.

42. (Cancelled)

43. (Cancelled)

44. (Amended) A method according to claim 14, 16, or 41, wherein at least one of the samples is in liquid form.